

Exhibit

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	
HARALD BREIVIK, et al.)	Examiner: P.K. Sripada
Serial No.: 07/902,500)	Group Art Unit: 1202
Filed: June 23, 1992)	Attorney Docket No.
For: FATTY ACID COMPOSITION)	1526.100 Cont. I

The Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

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RULE 132 DECLARATION BY ROBERT G. ACKMAN

I, Robert G. Ackman, a resident of Dartmouth, Nova Scotia, do hereby declare as follows:

1) Qualifications:

I am a Research Professor at the Technical University of Nova Scotia, in the Canadian Institute of Fisheries Technology and Department of Food Science and Technology, with which I have been associated since 1979. My specialty is the chemistry of fats, oils, and lipids, a field in which I have worked for more than 40 years. I have a B.A. in Organic Chemistry from the University of Toronto (awarded in 1950), an M.Sc. from Dalhousie University (awarded in 1952), and a Ph.D. from the University of London (awarded in 1956).

Attached as Exhibit A is a copy of my curriculum vita, which accurately reports my scientific education, training, and experience.

2) Familiarity With Cornieri et al.
and Breivik Declaration:

I have carefully read and considered U.S. Patent No. 5,130,061 to Cornieri et al., a copy of which is attached as Exhibit B, as well as the August 12, 1994 Declaration by Dr. Harald Breivik, a copy of which is attached as Exhibit C. The work with fish oil products that is reported in these documents is akin to work I have been doing for many years at the Canadian Institute of Fisheries Technology, and which is within my field of expertise.

3) Purpose of Review:

I was asked to review and evaluate the studies reported by Dr. Breivik in his Declaration, and to render an opinion on the following questions:

a) Given his stated objectives (page 2, lines 6-11), was the procedure Dr. Breivik followed (as reported in his Declaration) in his attempt to replicate the examples in Cornieri et al. logical and correct?

b) Were the results credible?

c) Are Dr. Breivik's conclusions (page 10, paragraph 3) reasonable?

4) Conclusions:

In my expert opinion:

a) The procedure Dr. Breivik reported using was logical and correct.

b) The results Dr. Breivik reported obtaining are credible.

c) The conclusions Dr. Breivik reached are reasonable.

5) Additional Observations:

Dr. Breivik accurately describes the replication of Cornieri et al. in his Example 2 preparation of ethyl esters. The oil used is probably menhaden oil. The % areas for the fatty acids listed total ^{89.6 %} ~~82.5~~%, and thus are a reasonable simplification of the actual composition made up of 40-50 individual fatty acids.

The purification of this product by "stripping" the esters at reduced pressure and 108° C is accurately described by Breivik and is very close to the conditions used by Cornieri et al. The distillation equipment is understood to be Leybold-Heraeus, similar to that employed by Cornieri et al.

It is questionable if Cornieri's claim of "molecular distillation" at 10^{-3} mm of mercury is valid. True "molecular distillation" is normally conducted at 10^{-6} mm of mercury and depends on the mean free path of the molecule in the vacuum being sufficient to reach a cooled condenser without colliding with any residual gas molecules. Similar molecules of greater molecular weight may be projected from the heated surface but will not reach the condenser (see Perry and Chilton, *Chemical Engineer's Handbook*, McGraw-Hill,

1973, attached Exhibit D). At higher pressures (10^{-3} mm of Hg as described in Cornieri et al.) it is better to refer to the process as "short-path" distillation. The theory of distillation in any unit gives one theoretical plate from a simple distilling surface to a single condenser. In the Leybold-Heraus and Pope equipment it appears that the mechanical equipment rotating within the distillation column (illustrated in Ackman, R.G., *Chemistry and Industry*, March 7, 1988, pp. 139-145, attached Exhibit E) gives some "reflux" effect as the esters descend the column, since the film is not a layer of consistent composition, but is constantly renewed by the roller or wiping effects. Only this "reflux" makes the series of "stripping" operations described in Cornieri et al. at all effective.

However, since the objective was to replicate the procedures of Cornieri et al., this use of inexact terminology is not relevant in evaluating the declaration by Breivik. The results from Porsgrunn and Sandefjord are stated in the text to be "products" and are accurately defined as residue and distillate. The accompanying text table refers to the composition of Porsgrunn residue 851-4, but Sandefjord obtained comparable results. The shift in proportions of EPA and DHA from 1.36:1 in the raw material to 1.15:1 in the residue with a percentage recovery of 69.3 (w/w, Table 1) is to be expected, given that the volatility of EPA is greater than that of DHA.

The series of distillation steps reported by Breivik is comparable to the Cornieri et al. Examples 4-7, with area % analyses of the residues, and is essentially logical and reasonable. In effect, the original objective of Cornieri et al. was to remove C_{14} , C_{16} and C_{18} materials by "stripping" at increasing temperatures while minimizing loss of C_{20} material (EPA). Since the short path distillations are inherently inefficient, compared to conventional distillations with packed or spinning-band distillation columns, there is no other option than repeating the operation several times. The temperatures for more conventional distillation can approach 200°C or more, damaging the natural PUFA (polyunsaturated fatty acid) structures, as described in my paper in *Chemistry and Industry* (Exhibit E). Breivik recognized the potential for oligomer (polymer) formation, but the moderate temperatures used ($\leq 125^{\circ}\text{C}$) would not be damaging to the PUFA structures in the absence of oxygen.

The tables presented by Breivik for ethyl ester compositions are clear in distinguishing areas (A) and weight (W) percentages. In my experience with urea complexation, a small percentage of the EPA is lost if the urea step is forced too far. By comparison, the DHA is unaffected. This is responsible for the change in EPA:DHA ratio from 0.34:1 to 0.25:1 (851.33 to 851.39-I) during urea complexation. The 0.25:1 is pre-distillation, so this effect is that of urea alone. The distillation (Breivik in-text table) has a minor

effect on both total % (of EPA+DHA) and on the EPA:DHA ratio, but the true weight % of 52-55% EPA+DHA ethyl esters is in accord with my experience. Although slightly lower than some published results (Ratnayake et al., *Fat. Sci. Technol.* 1988, Vol. 90, pp. 381-386, attached Exhibit F), the exact yield will be sensitive to starting material components as well as any polymers present in the products.

The DPA of Table 2 as A% is 15% of the DHA, which would add 8% (actual) to the total of 53% (for EPA+DHA). It is possible to speculate that Cornieri et al. used poor quality GC and included the n-3 DPA in their DHA. Under the "We claim:" first paragraph in Cornieri et al., the "DPA" is clearly an error for DHA. Their DPA would presumably be close to 10% of their DHA after all of these steps, subject to some loss in the urea treatment, since the first ethylenic bond is in the 7,8 position, encouraging some urea complexation. Their final DHA claim of 96% probably should then actually be $\leq 90\%$ based on their own measurement of GC volatile materials. DHA concentration was not their original objective, as EPA was included in the desired product.

Conclusions

Dr. Breivik made all reasonable efforts to duplicate the conditions set forth in U.S. Patent 5,130,061. The duplication of results from two different geographical locations enhances the validity of his findings.

The findings of Dr. Brevik include mass yields and other factors not given in U.S. Patent 5,130,061. Dr.

Breivik's company participated in an interlaboratory trial of a gas chromatography method published by the Association of Official Analytical Chemists as a first action in the Association's making this method official. The operating conditions of the Association of Official Analytical Chemists provide superior and acceptable results, whether area % or weight % results, as compared to those probably used by Cornieri et al.

The results obtained by Dr. Breivik and his colleagues are substantially in agreement with published results obtained in my laboratory using different procedural routes (e.g., urea complexing as a first concentration step) but achieving essentially the same 50-60% concentration of EPA+DHA (as ethyl esters). Total n-3 fatty acids can include 18:4n-3 and 22:5n-3, usually adding approximately another 10% to give 60-70%. The Cornieri et al. approach of reducing the mass by stepwise elimination of lower molecular weight esters will however eliminate the 18:4n-3. However, without mass and yield data it is impossible to evaluate the practicality of U.S. Patent 5,130,061.

6) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed by me to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of any patent that might issue on the above-identified application.

Date: Sept. 1, 1994

Halifax, Nova Scotia

R. G. Ackman
Robert G. Ackman

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